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http://dx.doi.org/10.1016/j.jacc.2013.03.024

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Body Mass Index, Central Obesity, and Mortality Among Coronary Disease Subjects

In their recent study, Coutinho et al. (1) concluded that normal body mass index with central obesity was associated with the highest risk of mortality in subjects with coronary artery disease. However, there is an uncertainty in interpreting the results of this study.

It is well known that medication use such as chronic statin therapy is closely associated with overall mortality in subjects with coronary artery disease or other cardiovascular diseases such as stroke and that subjects with obesity are more likely to be treated by use of medication such as chronic statin therapy because of metabolic abnormalities. In the study by Coutinho et al. (1), however, medication use such as chronic statin therapy was not described in detail, and the development of parsimonious Cox model was not adjusted for medication use such as chronic statin therapy. That is to say, medication use such as chronic statin therapy was not discussed in detail, which could have confounded the relationship of obesity to mortality in subjects with coronary artery disease. In addition, many other factors, which are well known to confound the relationship of obesity to mortality in subjects with coronary artery disease or other cardiovascular diseases such as stroke—for example, including but not limited to the history of change of weight, the condition of diet, weight loss, psychosocial stress, socioeconomic status, and physical activity—were not described in detail in the study by Coutinho et al. (1). Therefore it is unclear whether normal body mass index with central obesity is associated with the highest risk of mortality in subjects with coronary artery disease when the above-mentioned factors, which might confound the relationship of obesity to mortality, are taken into account.

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http://dx.doi.org/10.1016/j.jacc.2013.02.068

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Reply

We thank Profs. Song, Wang, and Zhang for their interest in our study (1).

Because our study was a meta-analysis with individual patient data, information on statins was not uniformly available in all studies included, and for this reason the use of statins was not originally included in the models as a potential confounder. Multivariable Cox proportional hazard models in the 6,313 of the 15,547 participants with data on statin use and including statin use as covariate showed that normal-weight central obesity still had the highest mortality among all participants (analyses not shown). Furthermore, in the setting of secondary prevention, the relative risk reduction attributed to statins is approximately 20% (2), representing an association of lesser magnitude than the increased risk found with normal-weight central obesity. Thus, it is unlikely that the results of our study were driven by differences in statin use among subjects with different body adiposity patterns.

We recognize that there might be some residual confounding attributed to differences among groups in weight change over time, diet, psychosocial stress, socioeconomic status, and physical activity. Unfortunately, we had limited information on these factors to completely adjust in the multivariate models. However, we are not aware of any evidence suggesting that subjects with normal-weight central obesity would be more stressed, poorer, less likely to lose weight, or have worse nutrition than people with general obesity or other patterns of fat distribution, to suspect that these variables would explain all of the association between normal-weight central obesity and higher mortality.

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http://dx.doi.org/10.1016/j.jacc.2013.03.027

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Pitfall of the Meta-Analysis Regarding Early Repolarization Pattern

We read with much interest the paper published by Wu et al. (1). The paper summarized previous papers dealing with early repolarization pattern (ERP). In their meta-analysis, epidemiological studies regarding ERP were selected to examine whether ERP was associated with cardiac mortality in the general population. Although they selected suitable studies, several questions arise in their data analyses and interpretations.

First, we are concerned that the authors overestimated the results of "death from cardiac cause" in their meta-analysis. We have carefully reviewed the risk ratios and corresponding person-years and events of each study in Figure 2 of their paper (1). Although it is noted that "total" represents person-years in the annotation, the numbers in the "total" column did not present the values of person-years in "death from cardiac cause." Indeed, the numbers in this "total" column correspond exactly to the numbers of subjects with ERP or subjects without ERP in each study cited. Because of these errors, the risk ratios that the authors calculated were much lower than hazard ratios reported in some studies. For example, the risk ratio for "death from cardiac cause" is unrealistically low compared with that in the study of Haruta et al. (2). We were concerned that the procedure used to analyze "death from cardiac cause" was apparently different from those used for "death from all causes" and "death from arrhythmia."

Second, we are concerned about the different clinical outcomes used to analyze "death from arrhythmia." Haruta et al. (2) studied an association between ERP and "unexplained death," and Olson et al. (3) set sudden cardiac death as an endpoint. In these studies, whether or not arrhythmic death occurred was not clarified. Therefore, including the results of these two studies in the part of "death from arrhythmia" may cause overestimation of the risk ratios for arrhythmic death.

Third, the definition of *ERP* was not consistent among the studies. ERP was identified when J-point elevation was present in at least two leads in most studies, whereas J-point elevation in any lead was used to identify ERP in the study by Olson et al. (3). Thus, comparing the risk ratios of these studies does not yield an accurate conclusion. In addition, Haruta et al. (2) included Brugada-type electrocardiographic findings in ERP, which may increase the incidence of unexplained death. Therefore, caution is required in interpreting ERP as a potential phenotype as is stated by Wu et al. (1).

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Reply

We read the letter from Dr. Hayashi and colleagues and checked our data carefully (1). We found an error in the "total" columns. The "total" columns in our paper are subjects with and without ERP, not person-years. However, the overall estimated effect did not change when we re-estimated the overall effect for "death from cardiac cause" using person-years instead of subjects. According to our re-estimated effect, we also did not overestimate the results of "death from cardiac cause" in our meta-analysis. We are sorry for the error.

We did not overestimate the risk ratios for arrhythmic death. The study population in the paper by Olson et al. (2) came from the ARIC (Atherosclerosis Risk in Communities) study, and *sudden cardiac death* means arrhythmia-related death *Unexplained death* in the paper by Haruta et al. (3) included unexplained accidental death and sudden death, generally meaning arrhythmia-related death.

Early repolarization pattern (ERP) was characterized by an elevation ≥0.1 mV of the QRS-ST junction (J point) in the inferior and/or lateral leads on 12-lead electrocardiography. Also, we limited ERP to either QRS notching or slurring in our meta-analysis, which was different from the QRS morphology of Brugada syndrome. So, we did not overestimate the risk ratios for arrhythmic death owing to including some patients with Brugada syndrome.

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